REMARKS

These remarks are in response to the Office Action mailed January 9, 2004. Claims 1 to 39 are pending. Claim 11 stands withdrawn as being directed to a non-elected invention. By the present amendment, claims 5 and 22 have been cancelled without prejudice. Applicants maintain the right to prosecute the cancelled claims in any related application claiming the benefit of priority of the subject application. New claim 40, which depends from claim 13, has been added. Accordingly, upon entry of the amendment, claims 1 to 4, 6 to 10, 12 to 21, 23 to 25 and 28 to 40 are under consideration. Applicants respectfully request reconsideration of the application.

Regarding the Claim Amendments and New Claim

The amendments to the claims are supported throughout the specification or were made to address informalities. In particular, the amendments to claims 1 and 12 to 14 to delete the term "or" was made to define the claimed methods with greater particularity, which are performed prior to "formation of inhibitory antibodies." The amendment to claim 6 to recite "encoding said blood coagulation protein" was made in order to more clearly indicate that the nucleic acid encodes the blood coagulation protein to be delivered to the mammal. The amendment to claim 8 to depend from claim 3 instead of claim 5 was necessitated by the cancellation of claim 5. The amendment to claim 12 to recite "mammal" is supported, for example, by originally filed claims 1 and 3; at page 10, lines 25-26; at page 13, lines 13-15; at page 13, line 29, to page 14, line 3; and at page 16, lines 1-6. The amendment to claim 17 to depend from new claim 40 instead of claim 18 was made to correct an obvious error in claim dependency. The amendment to claim 18 to depend from claim 16 instead of claim 17 was also made to correct an obvious error in claim dependency. The amendment to claim 25 to depend from claim 12 instead of claim 13, and to delete the recitation of "blood coagulation" was made to correct an obvious duplicate claim and to provide adequate antecedent basis. Thus, as the claim amendments are supported by the specification or were made to address informalities, no new matter has been added and entry thereof is respectfully requested.

New claim 40 substantially parallels claim 6 and is therefore supported by originally filed claim 6. Thus, as new claim 40 is supported by the specification, no new matter has been added and entry thereof is respectfully requested.

I. CLAIM OBJECTIONS

The Examiner indicates that claims 3 and 5, 12 and 14, 20 and 22, and 23 and 25, respectively, are substantial duplicates and the latter claims will be objected to under 37 C.F.R. §1.75 should the former claims be allowed. By the present Response, claims 5 and 22 have been cancelled herein without prejudice rendering the objection moot. Claims 12 and 25 have been amended so that they are no longer substantial duplicates of claims 14 and 23, respectively. As such, Applicants respectfully request that the objection be withdrawn.

II. REJECTIONS UNDER 35 U.S.C. §112

The rejection of claims 6, 17 and 18 under 35 U.S.C. §112, second paragraph, as allegedly indefinite is respectfully traversed. The Examiner indicates that claim 6 allegedly is incomplete as omitting essential steps. Claims 17 and 18 are indicated to be indefinite since they depend from each other.

Claim 6 has been amended to recite that the nucleic acid encodes the blood coagulation factor to be delivered to the mammal. As such, claim 6 is clear and definite.

Claim 17 has been amended to depend from claim 40 and claim 18 has been amended to depend from claim 16. As such, claims 17 and 18 are clear and definite.

Accordingly, in view of the amendments, claims 6, 17 and 18 are clear and definite. As such, Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

III. REJECTIONS UNDER 35 U.S.C. §103(a)

Wilson et al., Bach and Tripathy et al.

The rejection of claims 1 to 6, 10, 12 to 16, 19, 20, 22, 28 to 33, 35, 37 and 38 under 35 U.S.C. §103(a) as allegedly unpatentable over Wilson *et al.* (U.S. Patent No. 6,251,957) in

further view of Bach (WO 96/25177) and Tripathy *et al.* (Nat. Med. 2:545 (1996)) is respectfully traversed.

Claims 5 and 22 have been cancelled herein without prejudice. Accordingly, the rejection is moot in respect to these claims. As to claims 1 to 4, 6, 10, 12 to 16, 19, 20, 28 to 33, 35, 37 and 38, prior to the present Response these claims would not have been obvious in view of Wilson *et al.* alone, or in any combination with Bach and Tripathy *et al.* Nevertheless, solely in order to further prosecution of the subject application, and without acquiescing to the propriety of the rejection, the claims have been amended as set forth above. The rejection will therefore be addressed in respect to the amended claims.

In order for a rejection to be proper under 35 U.S.C. §103, *inter alia*, there must have been a suggestion or motivation to modify or combine the references at the time of the invention; the combination of references must teach or suggest each and every element of the claimed invention; and there must have been a reasonable expectation of success at the time of the invention. Both the teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, not in Applicants' disclosure. See, e.g., *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991) and *In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988). Furthermore, the prior art must be considered in its entirety....including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983).

Here, *inter alia*, there would not have been any motivation to combine or modify the cited references to produce the claimed methods, nor a reasonable expectation of success of producing the claimed methods, in view of Wilson *et al.*, Bach and Tripathy *et al.* alone, or in any combination, at the time of the invention. Moreover, the cited Tripathy *et al.* reference and Herzog *et al.* (Blood 90, part 1, Supp. 1, abstract 1057 (1997), referred to herein as "Herzog Blood") both teach away from the claimed methods.

Claims 1 to 4, 6 to 10, 12 to 21, 23 to 25 and 28 to 40 are directed to methods of preventing or reducing formation of an inhibitory antibody to a blood coagulation protein or a protein delivered by way of gene therapy. The claimed methods require, *inter alia*, that an immunosuppressive agent be administered prior to or simultaneously with the gene therapy

"before formation of said inhibitory antibodies." The claimed methods also require, *inter alia*, delivery of a blood coagulation protein or a protein which is the "same species" as the mammal to which it is delivered.

Wilson *et al.* describe a recombinant adenovirus expressing human placental ALP gene and infecting mice with this recombinant adenovirus (see, for example, column 11, lines 52-59). The mice were also administered either antibody to CD4+ cells, Il-12 or gamma interferon (page 12, lines 17-31). Mice treated with antibody to CD4+ cells, Il-12 or gamma interferon exhibited higher levels of ALP expression than controls (column 12, line 55, to column 13, line 2). Wilson *et al.* also describe a recombinant adenovirus expressing human LDL receptor gene and infecting mice with this adenovirus (see, for example, column 17, lines 40-45; and Kozarsky *et al.*, J. Biol. Chem. 269:13695 (1994)). However, in contrast to the claimed methods, the genes delivered to the mice were human, and were not the same species. Nowhere do Wilson *et al.* teach or suggest delivering a blood coagulation protein or a protein by way of gene therapy that is the same species as the mammal to which it is delivered.

Furthermore, Wilson *et al.* indicate that the their method is for reducing immune response against a viral gene therapy vector (see, for example, abstract; column 2, lines 36-44; column 4, lines 35-39; and column 6, lines 16-19). Nowhere do Wilson *et al.* teach or suggest that an immune response is produced against the protein delivered by way of gene therapy, let alone an immune response against a protein that is the same species as the mammal to which it is delivered, as in claims 1 to 4, 6, 10, 12 to 16, 19, 20, 28 to 33, 35 and 37 to 40. Absent such a teaching or suggestion, the skilled artisan would not have been motivated to administer an immunosuppressive agent prior to or simultaneously with gene therapy to deliver a blood coagulation protein or a protein which is the same species as the mammal prior to the mammal forming inhibitory antibodies against the blood coagulation protein or protein.

Bach (WO 96/25177, U.S. counterpart Patent Publication No. 2003/0004091) describes adenovirus expressing a gene along with an immunoprotective gene (immunosuppressive agent; see, for example, [0012] and [0016]). Bach is identical to Wilson *et al.* in that the gene in the adenovirus, bacterial beta-galactosidase, is not the same species as the animal, a mouse, to which it is delivered (see, for example, [0098], [0125] and [0145]). Nowhere does Bach teach or

suggest delivering a gene by way of gene therapy that encodes a protein that is the same species as the mammal to which the gene is delivered.

Bach is also identical to Wilson *et al.* in that the "invention is directed towards preventing the rapid elimination of adenoviruses from the infected cells and hence towards prolonging, in a consistent manner, the in vivo expression of the therapeutic gene which they are carrying." (see, for example, [0010]). Nowhere does Bach teach or suggest that an immune response against a protein delivered by way of gene therapy is produced, let alone an immune response against a protein that is the same species as the mammal to which it is delivered. Absent such a teaching or suggestion, the skilled artisan would not have had any reason to administer an immunosuppressive agent prior to or simultaneously with gene therapy to deliver a blood coagulation protein or a protein which is the same species as the mammal prior to the mammal forming inhibitory antibodies against the blood coagulation protein or a protein.

Tripathy *et al.* describe using replication defective adenovirus for gene therapy. In brief, mice were injected with adenovirus having a gene that encoded a murine or a human erythropoietin (EPO) (see, for example, abstract). Tripathy *et al.* indicate that mice injected with adenovirus harboring the human EPO developed anti-EPO antibodies whereas mice injected with adenovirus harboring the murine EPO did not develop anti-EPO antibodies (see, for example, page 548, left column, first paragraph). However, nowhere does Tripathy *et al.* teach or suggest that an immune response is produced against a protein delivered by way of gene therapy when the protein is the same species as the mammal to which it is delivered. Absent such a teaching or suggestion, the skilled artisan would have had no reasons to administer an immunosuppressive agent prior to or simultaneously with gene therapy to deliver a blood coagulation protein or a protein which is the same species as the mammal prior to the mammal forming inhibitory antibodies against the blood coagulation protein or a protein.

Moreover, because murine EPO delivered by way of gene therapy did NOT induce an immune response in the mice to which it was delivered, Tripathy *et al.* teach away from the claimed methods. In this regard, no immune response was elicited in the mice when the murine EPO was delivered to the mouse via gene therapy. Consequently, the skilled artisan would not have administered an immunosuppressive agent prior to or simultaneously with gene therapy

when the gene delivered encodes a protein that is the same species as the mammal to which it is delivered, because to do so would be pointless.

Analogous to Tripathy *et al.*, Herzog Blood also teach away from the claimed methods. In this regard, Herzog Blood describe data demonstrating that administering a gene therapy vector encoding a protein that is the same species as the animal to which it is delivered did not elicit an immune response against the protein. In view of the fact that two independent investigators at the time of the invention found that administering a gene therapy vector encoding a protein that is the same species as the animal did not elicit an immune response against the protein, the skilled artisan would not use an immunosuppressive agent prior to or simultaneously with gene therapy when the gene encodes a protein that is the same species as the mammal to which it is delivered. Consequently, Tripathy *et al.*, and Herzog Blood both teach the skilled artisan away from producing the claimed methods.

Finally, with regard to the statement in the Office Action at page 7, allegedly that "Tripathy, Wilson, and Bach teach that exposure of a novel human protein by way of gene therapy to a human deficient for the protein results in an immune response against the protein," Applicants respectfully disagree. As discussed above, no such teaching exists in any of Wilson *et al.*, Bach or Tripathy *et al.* alone, or in any combination. In fact, both Tripathy *et al.* and Herzog Blood teach the opposite: administering a gene therapy vector encoding a protein that is the same species as the animal to which it is administered does NOT elicit an immune response in the animal. Because both Tripathy *et al.* and Herzog Blood are contrary to the claimed methods, clearly the claims would not have been obvious in view of Wilson *et al.*, Bach and Tripathy *et al.* alone, or in any combination, at the time of the invention

In sum, in view of the fact that none of Wilson *et al.*, Bach or Tripathy *et al.* alone, or in any combination, teach or suggest that an immune response is elicited in an animal when the protein delivered by way of gene therapy is the same species as the animal to which is delivered, the cited references fail to provide the requisite motivation to produce claims 1 to 4, 6, 10, 12 to 16, 19, 20, 28 to 33, 35 and 37 to 40. In further view of the fact that Tripathy *et al.* and Herzog Blood teach that administering a gene therapy vector encoding a protein that is the same species as the animal to which it is delivered does not elicit an immune response, one skilled in the art would not have administered an immunosuppressive agent prior to or simultaneously with gene

therapy when the gene delivered encodes a protein that is the same species as the mammal to which it is delivered.

In view of the foregoing, claims 1 to 4, 6, 10, 12 to 16, 19, 20, 28 to 33, 35 and 37 to 40 would not have been obvious over Wilson *et al.* in view of Bach and Tripathy *et al.* at the time of the invention. Consequently, the rejection under 35 U.S.C. §103(a) over Wilson *et al.* (U.S. Patent No. 6,251,957) in view of Bach (WO 96/25177) and Tripathy *et al.* (Nat. Med. 2:545 (1996)) is improper and must be withdrawn.

Wilson et al., Bach, Tripathy et al., Nilsson et al. and Warrier et al.

The rejection of claims 1, 12, 13, 14, 23 to 25 and 39 under 35 U.S.C. §103(a) as allegedly unpatentable over Wilson *et al.* (U.S. Patent No. 6,251,957) with Bach (WO 96/25177) and Tripathy *et al.* (Nat. Med. 2:545 (1996)) in further view of Nilsson *et al.* (Proc. Natl. Acad. Sci. USA 83:9169 (1986)) and Warrier *et al.* (Blood Coag. Fibrinol. 9(Suppl 1):S125 (1998)) is respectfully traversed.

Claims 1, 12, 13, 14, 23 to 25 and 39 prior to the present Response would not have been obvious in view of Wilson *et al.*, Bach, Tripathy *et al.*, Nilsson *et al.*, or Warrier *et al.* alone, or in any combination. Nevertheless, solely in order to further prosecution of the subject application, and without acquiescing to the propriety of the rejection, the claims have been amended as set forth above. The rejection will therefore be addressed in respect to the amended claims.

The deficiencies of Wilson *et al.*, Bach and Tripathy *et al.* are described above. In brief, neither Wilson *et al.*, Bach or Tripathy *et al.* alone, or in any combination, teach or suggest that an immune response is elicited in an animal when the protein delivered by way of gene therapy is the same species as the mammal to which is delivered. Consequently, the skilled artisan would have no motivation to produce the claimed methods. Furthermore, because both Tripathy *et al.* and Herzog Blood teach that a gene therapy vector encoding a protein that is the same species as the animal to which it is delivered does not elicit an immune response, the skilled artisan would not have administered an immunosuppressive agent prior to or simultaneously with gene therapy when the gene delivered encodes a protein that is the same species as the mammal

to which it is delivered. Consequently, both Tripathy *et al.* and Herzog Blood teach away from producing the claimed methods.

Neither Nilsson *et al.*, or Warrier *et al.* correct the deficiencies of Wilson *et al.*, Bach and Tripathy *et al.* In particular, Nilsson *et al.* describe studies in which hemophiliacs that produce antibodies against factor IX were treated with high doses of IgG with cyclophosphamide and factor IX (see, for example, abstract). Nilsson *et al.* indicate that all three components together can induce tolerance (see, for example, page 9172, left column, first paragraph under *Discussion*). However, Nilsson *et al.* do not teach or suggest that an immune response is elicited in an animal when a protein delivered by way of gene therapy is the same species as the mammal to which is delivered. In this regard, gene therapy is not even mentioned in Nilsson *et al.*

Nilsson *et al.* also fail to teach or suggest treating hemophiliacs prior to formation of inhibitory antibodies. In this regard, all four hemophiliacs treated had already developed inhibitory antibodies against factor IX, and Nilsson *et al.* do not mention treating hemophiliacs prior to formation of inhibitory antibodies. Consequently, Nilsson *et al.* does not provide any motivation to treat hemophiliacs prior to formation of inhibitory antibodies, let alone in the manner claimed.

Warrier *et al.* describe factor IX inhibitors, which are present in hemophiliacs and are associated with the total absence of factor IX antigen due to FIX deletions or other major rearrangements (see abstract). Here, as with the four other cited references, Warrier *et al.* fail to teach or suggest that an immune response is elicited in an animal when a protein delivered by way of gene therapy is the same species as the mammal to which is delivered. In this regard, Warrier *et al.* describe several hypothetical reasons for the development of inhibitors (page S126, left column). One hypothesis, which the authors state "is an attractive one to consider" is that there is a deletion of neighboring genes that modulate the immune response (page S126, left column, third full paragraph). Thus, since Warrier *et al.* clearly does not understand why inhibitors form, this reference cannot objectively be said to teach, suggest or motivate the skilled artisan to administer an immunosuppressive agent prior to or simultaneously with gene therapy to deliver a blood coagulation protein or a protein which is the same species as the mammal prior to the mammal forming inhibitory antibodies against the blood coagulation protein or a protein, as is claimed.

As with Nilsson *et al.*, Warrier *et al.* also fail to teach or suggest treating hemophiliacs prior to formation of inhibitory antibodies. In this regard, although Warrier *et al.* suggest molecular diagnosis to identify children at greatest risk of severe hemophilia B, the only recommendation following diagnosis of large deletions or frameshift mutations of factor IX is to have them "monitored more closely during their first exposure to FIX." (page S127, right column, second full paragraph). Thus, Warrier *et al.* also fail to teach, suggest or provide any motivation to treat hemophiliacs prior to formation of inhibitory antibodies, let alone in the manner claimed.

Finally, as discussed above, Tripathy *et al.* and Herzog Blood describe data demonstrating that an animal administered a gene therapy vector encoding a protein that was the same species as the animal did not produce an immune response against the protein. In view of the fact that at least two independent investigators at the time of the invention found that a gene therapy vector encoding a protein that is the same species as the animal to which it was delivered did not elicit an immune response against the protein, the skilled artisan would have no reason to use an immunosuppressive agent prior to or simultaneously with gene therapy when the gene encodes a protein that is the same species as the mammal to which it is delivered. Again, because no immune response was elicited against the protein, it would be pointless to administer an immunosuppressive agent prior to or simultaneously with gene therapy. Consequently, each of Tripathy *et al.*, and Herzog Blood teach the skilled artisan away from the claimed methods.

In view of the foregoing, claims 1, 12, 13, 14, 23 to 25 and 39 would not have been obvious over Wilson *et al.*, Bach, Tripathy *et al.*, Nilsson *et al.* and Warrier *et al.* at the time of the invention. Consequently, the rejection under 35 U.S.C. §103(a) over Wilson *et al.* (U.S. Patent No. 6,251,957) with Bach (WO 96/25177) and Tripathy *et al.* (Nat. Med. 2:545 (1996)) in view of Nilsson *et al.* (Proc. Natl. Acad. Sci. USA 83:9169 (1986)) and Warrier *et al.* (Blood Coag. Fibrinol. 9(Suppl 1):S125 (1998)) is improper and must be withdrawn.

Wilson et al., Bach, Tripathy et al. and Herzog et al.

The rejection of claims 1, 6 to 8, 12, 14 and 33 to 36 under 35 U.S.C. §103(a) as allegedly unpatentable over Wilson *et al.* (U.S. Patent No. 6,251,957) with Bach (WO 96/25177)

and Tripathy *et al.* (Nat. Med. 2:545 (1996)) in further view of Herzog *et al.* (Proc. Natl. Acad. Sci. USA 94:5804 (1997), referred to herein as "Herzog PNAS") is respectfully traversed.

Claims 1, 6 to 8, 12, 14 and 33 to 36 prior to the present Response would not have been obvious in view of Wilson *et al.*, Bach, Tripathy *et al.*, and Herzog *et al.* alone, or in any combination. Nevertheless, solely in order to further prosecution of the subject application, and without acquiescing to the propriety of the rejection, the claims have been amended as set forth above. The rejection will therefore be addressed in respect to the amended claims.

The deficiencies of Wilson *et al.*, Bach and Tripathy *et al.* have been discussed at length. In brief, neither Wilson *et al.*, Bach or Tripathy *et al.* alone, or in any combination, teach or suggest that an immune response is elicited in an animal when a protein encoded by a gene delivered by way of gene therapy is the same species as the mammal to which it is delivered. Consequently, since no immune response is elicited against a protein that is the same species, the skilled artisan would not have had any reason to produce the claimed methods at the time of the invention.

Herzog PNAS does not correct the deficiencies of Wilson *et al.*, Bach and Tripathy *et al.* In brief, Herzog PNAS describes injection of recombinant adeno-associated virus vector expressing human factor IX in hindlimb muscles of mice (abstract). The authors were not able to find factor IX in mice, and the mice developed antibodies against the human factor IX (abstract). These studies were followed up by injections into rag 1 mice, which lack functional B and T cells, and exhibited therapeutic levels of the human factor IX in plasma (abstract). However, as with all of the other five cited references, Herzog PNAS does not teach or suggest that an immune response is elicited in an animal when a protein delivered by way of gene therapy is the same species as the mammal to which it is delivered. Absent such a teaching or suggestion, the skilled artisan would not have had any reason to administer an immunosuppressive agent prior to or simultaneously with gene therapy when the gene delivered encodes a protein that is the same species as the mammal to which it is delivered.

Furthermore, because both Tripathy *et al.* and Herzog Blood teach that administering a gene therapy vector encoding a protein that is the same species as the animal to which it is delivered does not elicit an immune response, the skilled artisan would not administer an immunosuppressive agent prior to or simultaneously with gene therapy when the gene encodes a

protein that is the same species as the animal to which it is delivered. Consequently, both Tripathy *et al.* and Herzog Blood teach away from producing the claimed methods.

In view of the foregoing, claims 1, 6 to 8, 12, 14 and 33 to 36 would not have been obvious over Wilson *et al.*, Bach, Tripathy *et al.*, and Herzog *et al.* at the time of the invention. Consequently, the rejection under 35 U.S.C. §103(a) over Wilson *et al.* (U.S. Patent No. 6,251,957) with Bach (WO 96/25177) and Tripathy *et al.* (Nat. Med. 2:545 (1996)) in view of Herzog *et al.* (Proc. Natl. Acad. Sci. USA 94:5804 (1997)) is improper and must be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 1 to 4, 6 to 10, 12 to 21, 23 to 25 and 28 to 40 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-2212.

Respectfully submitted,

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